Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSPTAJDA1614

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page for STN Seminar Schedule - N. America
NEWS 2	DEC 01	ChemPort single article sales feature unavailable
NEWS 3	APR 03	CAS coverage of exemplified prophetic substances enhanced
NEWS 4	APR 07	STN is raising the limits on saved answers
NEWS 5	APR 24	CA/CAplus now has more comprehensive patent assignee information
NEWS 6	APR 26	USPATFULL and USPAT2 enhanced with patent assignment/reassignment information
NEWS 7	APR 28	CAS patent authority coverage expanded
NEWS 8	APR 28	ENCOMPLIT/ENCOMPLIT2 search fields enhanced
NEWS 9	APR 28	Limits doubled for structure searching in CAS REGISTRY
NEWS 10	MAY 08	STN Express, Version 8.4, now available
NEWS 11	MAY 11	STN on the Web enhanced
NEWS 12	MAY 11	BEILSTEIN substance information now available on STN Easy
NEWS 13	MAY 14	DGENE, PCTGEN and USGENE enhanced with increased limits for exact sequence match searches and introduction of free HIT display format
NEWS 14	MAY 15	INPADOCDB and INPAFAMDB enhanced with Chinese legal status data
NEWS 15	MAY 28	CAS databases on STN enhanced with NANO super role in records back to 1992
NEWS 16	JUN 01	CAS REGISTRY Source of Registration (SR) searching enhanced on STN

NEWS EXPRESS MAY 26 09 CURRENT WINDOWS VERSION IS V8.4,
AND CURRENT DISCOVER FILE IS DATED 06 APRIL 2009.

NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS LOGIN Welcome Banner and News Items

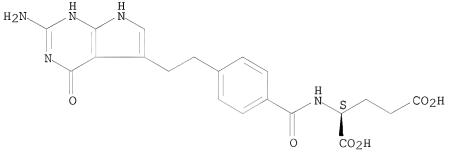
Enter NEWS followed by the item number or name to see news on that specific topic.

* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 16:01:52 ON 09 JUN 2009

```
=> file registry
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.22       0.22

FILE 'REGISTRY' ENTERED AT 16:02:08 ON 09 JUN 2009
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2009 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:    8 JUN 2009  HIGHEST RN 1154048-98-2
DICTIONARY FILE UPDATES:   8 JUN 2009  HIGHEST RN 1154048-98-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 9, 2009.

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> E "PEMETREXED"/CN 25
E1            1     PEMERID/CN
E2            1     PEMERID NITRATE/CN
E3            1 --> PEMETREXED/CN
E4            1     PEMETREXED CALCIUM/CN
E5            1     PEMETREXED DISODIUM/CN
E6            1     PEMETREXED DISODIUM HEPTAHYDRATE/CN
E7            1     PEMETREXED GLUCOSAMINE/CN
E8            1     PEMETREXED MAGNESIUM/CN
E9            1     PEMETREXED MEGLUMINE/CN
E10           1     PEMETREXED SODIUM/CN
E11           1     PEMEX/CN
E12           1     PEMEX 030/CN
E13           1     PEMEX 120/CN
E14           1     PEMEX 20020/CN
E15           1     PEMEX 20020X/CN
E16           1     PEMEX 6050/CN
E17           1     PEMEX 65050/CN
E18           1     PEMEX PX 20020X/CN
E19           1     PEMF 20/CN
E20           1     PEMF 35/CN
E21           1     PEMFLON/CN
E22           1     PEMI (CITROBACTER FREUNDII GENE PEMI)/CN
E23           1     PEMI PROTEIN (AGROBACTERIUM TUMEFACIENS STRAIN C58 GENE PEMI)/CN
E24           1     PEMI PROTEIN (BARTONELLA HENSELAE STRAIN HOUSTON-1 GENE PEMI)/CN
E25           1     PEMI PROTEIN (NEISSERIA MENINGITIDIS STRAIN MD58 GENE NMB0914)/CN

=> S E3
L1            1 PEMETREXED/CN

=> DIS L1 1 SQIDE
```

```
L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2009 ACS on STN
RN   137281-23-3  REGISTRY
CN   L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-3H-pyrrolo[2,3-
     d]pyrimidin-5-yl)ethyl]benzoyl]-  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   1H-Pyrrolo[2,3-d]pyrimidine, L-glutamic acid deriv.
CN   L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-
     d]pyrimidin-5-yl)ethyl]benzoyl]- (9CI)
OTHER NAMES:
CN   N-[4-[2-(2-Amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-
     yl)ethyl]benzoyl]-L-glutamic acid
CN   NSC 698037
CN   Pemetrexed
FS   STEREOSEARCH
MF   C20 H21 N5 O6
CI   COM
SR   CA
LC   STN Files:   ADISNEWS, AGRICOLA, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT,
       CBNB, CHEMCATS, CIN, DDFU, DRUGU, EMBASE, HSDB*, IMSDRUGNEWS,
       IMSPATENTS, IMSPRODUCT, IMSRESEARCH, IPA, MEDLINE, MRCK*, PATDPASPC,
       PHAR, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2,
       USPATFULL
         (*File contains numerically searchable property data)
DT.CA  CAplus document type:  Book; Conference; Dissertation; Journal; Patent
RL.P   Roles from patents:  ANST (Analytical study); BIOL (Biological study);
       PREP (Preparation); PROC (Process); PRP (Properties); PRPH (Prophetic);
       RACT (Reactant or reagent); USES (Uses)
RLD.P  Roles for non-specific derivatives from patents:  ANST (Analytical
       study); BIOL (Biological study); PREP (Preparation); PROC (Process);
       RACT (Reactant or reagent); USES (Uses)
RL.NP  Roles from non-patents:  ANST (Analytical study); BIOL (Biological
       study); PREP (Preparation); PROC (Process); PRP (Properties); RACT
       (Reactant or reagent); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents:  BIOL (Biological
       study); PREP (Preparation)

Absolute stereochemistry.
```




```
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

             512 REFERENCES IN FILE CA (1907 TO DATE)
              17 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             516 REFERENCES IN FILE CAPLUS (1907 TO DATE)


=> E "TETRAHYDROFOLATE"/CN 25
E1            1     TETRAHYDROFLUORAPHIN PERACETATE/CN
```

```
E2            1     TETRAHYDROFLUORENONE/CN
E3            0 --> TETRAHYDROFOLATE/CN
E4            1     TETRAHYDROFOLATE (PTERIDINE) DEHYDROGENASE/CN
E5            1     TETRAHYDROFOLATE DEHYDROGENASE/CN
E6            1     TETRAHYDROFOLATE DEHYDROGENASE (ESCHERICHIA COLI CLONE PLKO631
GENE DFR1 N-TERMINAL FRAGMENT)/CN
E7            1     TETRAHYDROFOLATE DEHYDROGENASE (ESCHERICHIA COLI STRAIN VA292
CLONE PDGO301 GENE DFRA7 TYPE VII)/CN
E8            1     TETRAHYDROFOLATE DEHYDROGENASE (ESCHERICHIA COLI)/CN
E9            1     TETRAHYDROFOLATE DEHYDROGENASE (XANTHOBACTER AUTOTROPHICUS GENE
MTDA)/CN
E10           1     TETRAHYDROFOLATE DEHYDROGENASE-LIKE PROTEIN 14 (HUMAN CLONE
PBS-0046D10)/CN
E11           1     TETRAHYDROFOLATE DEHYDROGENASE-THYMIDYLATE SYNTHASE (TETRAHYMENA
THERMOPHILA)/CN
E12           1     TETRAHYDROFOLATE DEHYDROGENASE/CYCLOHYDROLASE (1.5.1.5)
(LACTOCOCCUS LACTIS LACTIS STRAIN IL1403 GENE FOLD)/CN
E13           1     TETRAHYDROFOLATE DEHYDROGENASE/CYCLOHYDROLASE (ARTHROBACTER
AURESCENS STRAIN TC1)/CN
E14           1     TETRAHYDROFOLATE DEHYDROGENASE/CYCLOHYDROLASE (BRUCELLA
MELITENSIS BIOVAR ABORTUS STRAIN 2308 GENE FOLD)/CN
E15           1     TETRAHYDROFOLATE DEHYDROGENASE/CYCLOHYDROLASE (NITROBACTER
WINOGRADSKYI STRAIN NB-255)/CN
E16           1     TETRAHYDROFOLATE DEHYDROGENASE/CYCLOHYDROLASE (NITROSOMONAS
EUROPAEA STRAIN ATCC 19718 GENE FOLD)/CN
E17           1     TETRAHYDROFOLATE DEHYDROGENASE/CYCLOHYDROLASE (PSYCHROBACTER
ARCTICUS STRAIN 273-4 GENE FOLD)/CN
E18           1     TETRAHYDROFOLATE DEHYDROGENASE/CYCLOHYDROLASE (STREPTOCOCCUS
MUTANS STRAIN UA159 GENE FOLD)/CN
E19           1     TETRAHYDROFOLATE DEHYDROGENASE/CYCLOHYDROLASE, FOLD (CLOSTRIDIUM
ACETOBUTYLICUM STRAIN ATCC 824 GENE CAC2083)/CN
E20           1     TETRAHYDROFOLATE FORMYLASE/CN
E21           1     TETRAHYDROFOLATE METHYLTRANSFERASE/CN
E22           1     TETRAHYDROFOLATE REDUCTASE (HUMAN HERPESVIRUS 8)/CN
E23           1     TETRAHYDROFOLATE SYNTHASE/CN
E24           1     TETRAHYDROFOLATE SYNTHASE (YAMADAZYMA STIPITE STRAIN CBS 6054
GENE ADE3)/CN
E25           1     TETRAHYDROFOLATE SYNTHETASE/CN

=> file hcaplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                               8.36       8.58

FILE 'HCAPLUS' ENTERED AT 16:03:36 ON 09 JUN 2009
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2009 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 9 Jun 2009  VOL 150 ISS 24
FILE LAST UPDATED: 8 Jun 2009  (20090608/ED)
```

REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2009

HCAplus now includes complete International Patent Classification (IPC)
reclassification data for the third quarter of 2008.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s l1
L2   516 L1

=> s l2 and (CH2FH4 or FH4 or tetrahydrofolate or methyl-tetrahydrofolate or
methylene-tetrahydrofolate)
            26 CH2FH4
            65 FH4
          3308 TETRAHYDROFOLATE
            95 TETRAHYDROFOLATES
          3356 TETRAHYDROFOLATE
                 (TETRAHYDROFOLATE OR TETRAHYDROFOLATES)
       1102068 METHYL
           757 METHYLS
       1102518 METHYL
                 (METHYL OR METHYLS)
          3308 TETRAHYDROFOLATE
            95 TETRAHYDROFOLATES
          3356 TETRAHYDROFOLATE
                 (TETRAHYDROFOLATE OR TETRAHYDROFOLATES)
            83 METHYL-TETRAHYDROFOLATE
                 (METHYL(W)TETRAHYDROFOLATE)
        139426 METHYLENE
           926 METHYLENES
        139975 METHYLENE
                 (METHYLENE OR METHYLENES)
          3308 TETRAHYDROFOLATE
            95 TETRAHYDROFOLATES
          3356 TETRAHYDROFOLATE
                 (TETRAHYDROFOLATE OR TETRAHYDROFOLATES)
           647 METHYLENE-TETRAHYDROFOLATE
                 (METHYLENE(W)TETRAHYDROFOLATE)
L3   8 L2 AND (CH2FH4 OR FH4 OR TETRAHYDROFOLATE OR METHYL-TETRAHYDROFO
                LATE OR METHYLENE-TETRAHYDROFOLATE)

=> s "multi-targeting antifolate" or "multitargted antifolate"
        212463 "MULTI"
            11 "MULTIS"
        212471 "MULTI"
                 ("MULTI" OR "MULTIS")
         96122 "TARGETING"
            10 "TARGETINGS"
         96124 "TARGETING"
                 ("TARGETING" OR "TARGETINGS")
          1891 "ANTIFOLATE"
          1051 "ANTIFOLATES"
          2273 "ANTIFOLATE"
                 ("ANTIFOLATE" OR "ANTIFOLATES")
             1 "MULTI-TARGETING ANTIFOLATE"
                 ("MULTI"(W)"TARGETING"(W)"ANTIFOLATE")

```
            0 "MULTITARGTED"
         1891 "ANTIFOLATE"
         1051 "ANTIFOLATES"
         2273 "ANTIFOLATE"
                ("ANTIFOLATE" OR "ANTIFOLATES")
            0 "MULTITARGTED ANTIFOLATE"
                ("MULTITARGTED"(W)"ANTIFOLATE")
L4          1 "MULTI-TARGETING ANTIFOLATE" OR "MULTITARGTED ANTIFOLATE"

=> s "multi-targeting antifolate" or "multitargeted antifolate"
       212463 "MULTI"
           11 "MULTIS"
       212471 "MULTI"
                ("MULTI" OR "MULTIS")
        96122 "TARGETING"
           10 "TARGETINGS"
        96124 "TARGETING"
                ("TARGETING" OR "TARGETINGS")
         1891 "ANTIFOLATE"
         1051 "ANTIFOLATES"
         2273 "ANTIFOLATE"
                ("ANTIFOLATE" OR "ANTIFOLATES")
            1 "MULTI-TARGETING ANTIFOLATE"
                ("MULTI"(W)"TARGETING"(W)"ANTIFOLATE")
          380 "MULTITARGETED"
         1891 "ANTIFOLATE"
         1051 "ANTIFOLATES"
         2273 "ANTIFOLATE"
                ("ANTIFOLATE" OR "ANTIFOLATES")
          110 "MULTITARGETED ANTIFOLATE"
                ("MULTITARGETED"(W)"ANTIFOLATE")
L5          111 "MULTI-TARGETING ANTIFOLATE" OR "MULTITARGETED ANTIFOLATE"

=> s l5 and (CH2FH4 or FH4 or tetrahydrofolate or methyl-tetrahydrofolate or
methylene-tetrahydrofolate)
           26 CH2FH4
           65 FH4
         3308 TETRAHYDROFOLATE
           95 TETRAHYDROFOLATES
         3356 TETRAHYDROFOLATE
                (TETRAHYDROFOLATE OR TETRAHYDROFOLATES)
      1102068 METHYL
          757 METHYLS
      1102518 METHYL
                (METHYL OR METHYLS)
         3308 TETRAHYDROFOLATE
           95 TETRAHYDROFOLATES
         3356 TETRAHYDROFOLATE
                (TETRAHYDROFOLATE OR TETRAHYDROFOLATES)
           83 METHYL-TETRAHYDROFOLATE
                (METHYL(W)TETRAHYDROFOLATE)
       139426 METHYLENE
          926 METHYLENES
       139975 METHYLENE
                (METHYLENE OR METHYLENES)
         3308 TETRAHYDROFOLATE
           95 TETRAHYDROFOLATES
         3356 TETRAHYDROFOLATE
                (TETRAHYDROFOLATE OR TETRAHYDROFOLATES)
          647 METHYLENE-TETRAHYDROFOLATE
                (METHYLENE(W)TETRAHYDROFOLATE)
L6          2 L5 AND (CH2FH4 OR FH4 OR TETRAHYDROFOLATE OR METHYL-TETRAHYDROFO
```

LATE OR METHYLENE-TETRAHYDROFOLATE)

=> d l3 1-8 ibib, abs

L3 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:923137 HCAPLUS
DOCUMENT NUMBER: 148:372896
TITLE: Dose-dependent effects of (anti)folate preinjection on 99mTc-radiofolate uptake in tumors and kidneys
AUTHOR(S): Mueller, Cristina; Schibli, Roger; Forrer, Flavio; Krenning, Eric P.; de Jong, Marion
CORPORATE SOURCE: Department of Nuclear Medicine, Erasmus MC, Rotterdam, 3015 CE, Neth.
SOURCE: Nuclear Medicine and Biology (2007), 34(6), 603-608
CODEN: NMBIEO; ISSN: 0969-8051
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Introduction: The folate receptor (FR) is frequently overexpressed in tumors and can be targeted with folate-based (radio)pharmaceuticals. However, significant accumulation of radiofolates in FR-pos. kidneys represents a drawback. We have shown that preadministration of the antifolate pemetrexed (PMX) significantly improved the tumor-to-kidney ratio of radiofolates in mice. The aim of this study was to investigate the dose dependence of these effects and whether the same results could be achieved with folic acid (FA) or 5-methyl-tetrahydrofolate (5-Me-THF). Methods: Biodistribution was assessed 4 h postinjection of the organometallic 99mTc-picolylamine monoacetic acid folate in nude mice bearing FR-pos. KB cell tumor xenografts. PMX (50-400 μg/mouse) was injected 1 h previous to radioactivity. The effects of FA and 5-Me-THF (0.5-50 μg/mouse) were investigated likewise. Tissues and organs were collected and counted for radioactivity and the values tabulated as percentage of injected dose per g tissue (% ID/g). Results: PMX administration reduced renal retention (<1.6% ID/g vs. control: >10% ID/g), while the tumor uptake (average 1.35% ± 0.40% ID/g vs. control: 1.79% ± 0.49% ID/g) was only slightly affected independent of the PMX dose. Replacement of PMX by FA or 5-Me-THF (50 μg/mouse) resulted in a significant renal blockade (<0.1% ID/g) but at the same time in an undesired reduction of tumor uptake (<0.2% ID/g). Conclusions: Selective reduction of radiofolate uptake in kidneys under retention of high tumor accumulation could be achieved in combination with PMX over a broad dose range but not with FA or 5-Me-THF.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:654988 HCAPLUS
DOCUMENT NUMBER: 147:377847
TITLE: A Randomized, Double-Blind, Phase II Study of Two Doses of Pemetrexed as First-Line Chemotherapy for Advanced Breast Cancer
AUTHOR(S): Llombart-Cussac, Antonio; Martin, Miguel; Harbeck, Nadia; Anghel, Rodica M.; Eniu, Alexandra E.; Verrill, Mark W.; Neven, Patrick; De Greve, Jacques; Melemed, Allen S.; Clark, Romnee; Simms, Lorinda; Kaiser, Christopher J.; Ma, Doreen
CORPORATE SOURCE: Hospital Universitario Arnau Vilanova, Lleida, Spain
SOURCE: Clinical Cancer Research (2007), 13(12), 3652-3659
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB PURPOSE: Pemetrexed has shown varied response rates in advanced breast cancer. This randomized, double-blind, phase II study was conducted to assess the efficacy and safety of two doses of pemetrexed in a homogeneous population. A secondary objective was to identify mol. biomarkers correlating with response and toxicity. Exptl. DESIGN: Patients with newly diagnosed metastatic breast cancer or locally recurrent breast cancer received 600 mg/m2 (P600 arm) or 900 mg/m2 (P900 arm) of pemetrexed on day 1 of a 21-day cycle. All patients received folic acid and vitamin B12 supplementation. RESULTS: The P600 (47 patients) and P900 (45 patients) arms had response rates of 17.0% (95% confidence interval, 7.7-30.8%) and 15.6% (95% confidence interval, 6.5-29.5%) with .apprx.50% stable disease per arm, median progression-free survival of 4.2 and 4.1 mo, and median times to tumor progression of 4.2 and 4.6 mo, resp. Both arms exhibited minimal toxicity (grade 3/4 neutropenia <20%, leukopenia <9%, and other toxicities <5%). Tumor samples from 49 patients were assessed for the expression levels of 12 pemetrexed-related genes. Folylpolyglutamate synthetase and thymidine phosphorylase correlated with efficacy. Best response rates and median time to tumor progression for high vs. low thymidine phosphorylase expression were 27.6% vs. 6.3% (P = 0.023) and 5.4 vs. 1.9 mo (P = 0.076), and for folylpolyglutamate synthetase were 37.5% vs. 10.0% (P = 0.115) and 8.6 vs. 3.0 mo (P = 0.019), resp. γ-Glutamyl hydrolase expression correlated with grade 3/4 toxicities: 78.6% for high vs. 27.3% for low γ-glutamyl hydrolase (P = 0.024). CONCLUSION: The two pemetrexed doses yielded similar efficacy and safety profiles. Exploratory biomarker anal. identified efficacy and toxicity correlations and warrants further evaluation.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2006:1343787 HCAPLUS

DOCUMENT NUMBER: 146:197623

TITLE: A proposed clinical test for monitoring fluoropyrimidine therapy: detection and stability of thymidylate synthase ternary complexes

AUTHOR(S): Brody, Jonathan R.; Gallmeier, Eike; Yoshimura, Kiyoshi; Hucl, Tomas; Kulesza, Peter; Canto, Marcia I.; Hruban, Ralph H.; Schulick, Richard D.; Kern, Scott E.

CORPORATE SOURCE: Department of Oncology; The Sol Goldman Pancreatic Cancer Research Center and The Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

SOURCE: Cancer Biology & Therapy (2006), 5(8), 923-927 CODEN: CBTAAO; ISSN: 1538-4047

PUBLISHER: Landes Bioscience

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 5-Fluorouracil forms classic (covalent, ternary) complexes consisting of thymidylate synthase, fluoro-deoxyuridine monophosphate, and 5, 10-methylene tetrahydrofolate. Despite a high pharmacol. interest in the classic complexes formed in cells treated with fluorouracil anticancer agents, the in vivo stability of the complexes and the possible interference in complex formation by other coadministered compds. have not been adequately described. We visualized classic complexes unaccompanied by unbound thymidylate synthase, inferring complete enzymic inhibition, in 5-fluorouracil-treated S. cerevisiae and cancer cells in vitro and in murine tumors in vivo treated with 5-fluorouracil. Classic complexes persisted 13 days in cancer cells after a pulse of 5-fluorouracil. Classic complexes were reduced to absent in cancer cells in which the older antifolates methotrexate and aminopterin,

or the modern antifolates pemetrexed and tomudex, were coadministered with 5-fluorouracil. Classic complexes were, however, detected when an alternate drug, 5-fluorodeoxyuridine, was administered with methotrexate. We visualized classic complexes at fifteen minutes to seven days after an acute single dose of 5-fluorouracil in mouse tumor models, in tumors and normal tissues. Using the same assay, we detected unbound thymidylate synthase in untreated human tissues, supporting the future use of this assay in evaluating the most appropriate dose of fluoropyrimidine and coadministered agents in clin. settings.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:485104 HCAPLUS
DOCUMENT NUMBER: 145:431762
TITLE: Computer modelling of antifolate inhibition of folate metabolism using hybrid functional petri nets
AUTHOR(S): Assaraf, Yehuda G.; Ifergan, Ilan; Kadry, Wisam N.; Pinter, Ron Y.
CORPORATE SOURCE: Department of Biology, The Technion-Israel Institute of Technology, Technion, Haifa, 32000, Israel
SOURCE: Journal of Theoretical Biology (2006), 240(4), 637-647 CODEN: JTBIAP; ISSN: 0022-5193
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Antifolates are used in the treatment of various human malignancies and exert their cytotoxic activity by inhibiting folate-dependent enzymes resulting in disruption of DNA synthesis and cell death. Here we devised a computerized hybrid functional petri nets (HFPN) modeling of folate metabolism under physiol. and antifolate inhibitory conditions. This HFPN modeling proved valid as a good agreement was found between the simulated steady-state concns. of various reduced folates and those published for cell exts.; consistently, the simulation derived total folate pool size (11.3 μM) was identical to that published for cell exts. In silico expts. were conducted to characterize the inhibitory profile of four distinct antifolates including methotrexate (MTX), tomudex, and LY309887, which inhibit dihydrofolate reductase (DHFR), thymidylate synthase (TS) and glycineamide ribonucleotide transformylase (GARTFase), resp., as well as pemetrexed which has the capacity to inhibit all three enzymes. In order to assess the inhibitory activity of antifolates on purines and pyrimidines, the biosynthesis rates of IMP (20.53 μM/min) and dTMP (23.8 μM/min) were first simulated. Whereas the biochem. inhibitory profile of MTX was characterized by increased dihydrofolate and decreased tetrahydrofolate (THF) concns., the remaining antifolates did not decrease THF levels. Furthermore, MTX was 766- and 10-fold more potent in decreasing the production rates of IMP and dTMP, resp., than pemetrexed. LY309887 indirectly decreased the rate of dTMP production by reducing the levels of 5-CH2-THF, a folate cofactor for TS. Surprisingly, pemetrexed failed to inhibit DHFR even at high concns. This HFPN-based simulation offers an inexpensive, user-friendly, rapid and reliable means of pre-clin. evaluation of the inhibitory profiles of antifolates.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:601102 HCAPLUS
DOCUMENT NUMBER: 143:266886
TITLE: Synthesis of Classical, Four-Carbon Bridged 5-Substituted Furo[2,3-d]pyrimidine and 6-Substituted Pyrrolo[2,3-d]pyrimidine Analogues as Antifolates
AUTHOR(S): Gangjee, Aleem; Zeng, Yibin; McGuire, John J.;

Kisliuk, Roy L.
CORPORATE SOURCE: Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, PA, 15282, USA
SOURCE: Journal of Medicinal Chemistry (2005), 48(16), 5329-5336
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 143:266886

AB The biol. activities of four-carbon-atom bridged classical antifolates on dihydrofolate reductase (DHFR), thymidylate synthase (TS), and folylpolyglutamate synthetase (FPGS) as well as antitumor activity were reported. Extension of the bridge homologation studies of classical two-carbon bridged antifolates, a 5-substituted 2,4-diaminofuro[2,3-d]pyrimidine and a 6-substituted 2-amino-4-oxopyrrolo[2,3-d]pyrimidine, afforded two four-carbon bridged antifolates, analogs, with enhanced FPGS substrate activity and inhibitory activity against tumor cells in culture (EC50 ≤ 10-7 M) compared with the two-carbon bridged analogs. These results support an original hypothesis that the distance and orientation of the side chain p-aminobenzoyl-L-glutamate moiety with respect to the pyrimidine ring are a crucial determinant of biol. activity. In addition, this study demonstrates that, for classical antifolates that are substrates for FPGS, poor inhibitory activity against isolated target enzymes is not necessarily a predictor of a lack of antitumor activity.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:588673 HCAPLUS
DOCUMENT NUMBER: 143:91000
TITLE: Reduction of toxicity of multi-targeting antifolates
INVENTOR(S): Gustavsson, Bengt; Carlsson, Goeran
PATENT ASSIGNEE(S): Biofol AB, Swed.
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005060973	A1	20050707	WO 2004-SE1955	20041222
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2550298	A1	20050707	CA 2004-2550298	20041222
EP 1699462	A1	20060913	EP 2004-809128	20041222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				
JP 2007515482	T	20070614	JP 2006-546912	20041222

US 20070249613 A1 20071025 US 2007-583508 20070515
PRIORITY APPLN. INFO.: SE 2003-3526 A 20031222
WO 2004-SE1955 W 20041222

AB The use of tetrahydrofolate, methylene-tetrahydrofolate and/or methyl-tetrahydrofolate , and at least one multi-targeting antifolate, for the manufacture of a pharmaceutical composition for the treatment of cancer is disclosed. By combining the multi-targeting anti-folate with tetrahydrofolate, methylene-tetrahydrofolate and/or methyl-tetrahydrofolate, it is possible to remarkably reduce toxic side-effects without diminishing the antitumor action of the drugs. A pharmaceutical composition, a kit comprising the pharmaceutical composition as well as a method for the treatment of cancer are also disclosed. An example is give of multitargeting antifolate therapy in combination the the natural isome of methylenetetrahydrofolate in experiment adenocarcinoma in rats.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2004:363273 HCAPLUS
DOCUMENT NUMBER: 141:654
TITLE: Selective Preservation of Pemetrexed Pharmacological Activity in HeLa Cells Lacking the Reduced Folate Carrier: Association with the Presence of a Secondary Transport Pathway
AUTHOR(S): Zhao, Rongbao; Hanscom, Marie; Chattopadhyay, Shrikanta; Goldman, I. David
CORPORATE SOURCE: the Albert Einstein College of Medicine, Departments of Medicine and Molecular Pharmacology, The Einstein Cancer Research Center, Bronx, NY, 10461, USA
SOURCE: Cancer Research (2004), 64(9), 3313-3319
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A methotrexate (MTX)-resistant HeLa subline (R5), developed in this laboratory, with impaired transport due to a genomic deletion of the reduced folate carrier (RFC) was only 2-fold resistant to pemetrexed (PMX), but 200- and 400-fold resistant to raltitrexed (ZD1694) and Nα-(4-amino-4-deoxypteroyl)-Nδ-hemiphthaloyl-l-ornithine (PT523), resp., compared with parental HeLa cells when grown with 2 μM folic acid. When folic acid was replaced with the more physiol. 25 nM 5-formyltetrahydrofolate, R5 cells were 2-fold collaterally sensitive to PMX but still 40- and 200-fold resistant to ZD1694 and PT523, resp. Sensitivity to PT523 and PMX could be completely restored, and sensitivity to ZD1694 nearly restored, by transfection of RFC cDNA into R5 cells, indicating that the defect in drug transport was the only, or major, factor in resistance. The preserved PMX activity in R5 cells could not be related to the very low expression of folate receptors. Rather, retained PMX activity in R5 cells was associated with residual transport by another process that exhibits good affinity for PMX (Kt = 12 μM) with much lower affinities for ZD1694, MTX, and PT523 (Kis of .apprx. 90, 100, and 250 μM, resp.). PMX transported by this route was rapidly converted to higher polyglutamates and, when grown with 25 nM 5-formyl-tetrahydrofolate, the rate of formation of these derivs. and their net accumulation in R5 cells was comparable to that of wild-type cells. These data suggest that selective preservation of PMX pharmacol. activity in RFC-null R5 cells is due, in part, to partial preservation of transport by secondary process with a higher affinity for PMX than the other antifolates evaluated.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1995:743965 HCAPLUS
DOCUMENT NUMBER: 123:160281
ORIGINAL REFERENCE NO.: 123:28239a,28242a
TITLE: Mechanisms of resistance of N-[5-(N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino) -2-thenoyl]-L-glutamic acid (ZD1694), a folate-based thymidylate synthase inhibitor, in the HCT-8 human ileocecal adenocarcinoma cell line N-[5-(N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino)-2-thenoyl]-L-glutamic acid (ZD1694) is a folate-based thymidylate synthase (TS; EC 2.1.1.45) inhibitor.
AUTHOR(S): Lu, Kun; Yin, Ming-Biao; McGuire, John J.; Bonmasser, Enzo; Rustum, Youcef M.
CORPORATE SOURCE: Dep. Exp. Med. Biochem. Sci., Univ. Rome "Tor Vergata", Rome, 00133, Italy
SOURCE: Biochemical Pharmacology (1995), 50(3), 391-8
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Metabolism to higher chain length polyglutamates is essential for its optimal cytotoxic effect. A ZD1694-resistant (300-fold) human ileocecal carcinoma cell line (HCT-8/DW2) was developed, and its mechanism of resistance was evaluated. TS activities in situ and TS protein levels in the HCT-8 parental line and HCT-8/DW2 were similar (168 ± 47 vs. 137 ± 25 pmol/h/106 cells and 2.05 ± 0.28 vs. 2.07 ± 0.19 pmol/mg protein, resp.). The IC50 values of ZD1694 for TS inhibition in cell-free exts. were similar in both lines, but the IC50 of ZD 1694 for TS inhibition in situ in HCT-8/DW2 cells was 27- and 268-fold higher than that in HCT-8 cells at 0 and 24 h, resp., after a 2-h drug exposure. Folylpolyglutamate synthetase (FPGS; EC 6.3.2.17) activity was significantly lower in resistant HCT-8/DW2 cells as compared with parental HCT-8 cells (88 ± 40 vs. 1065 ± 438 pmol/h/mg protein when ZD 1694 was used as substrate). The combined endogenous pool of methylenetetrahydrofolate and tetrahydrofolate in HCT-8/DW2 cells was also decreased. In addition, HCT-8/DW2 cells accumulated lower levels of methotrexate (MTX) in a 2-h period, although the initial velocity of MTX transport was similar to that in parental HCT-8 cells. The lower level of FPGS activity and the lower level of (anti)folate accumulation in HCT-8/DW2 correlated with drug resistance and with the higher IC50 of ZD 1694 for in situ TS inhibition. In addition, drug resistance was also correlated with the rapid recovery of in situ TS activity after drug treatment. In brief, in this highly ZD1694-resistant HCT-8 cells line, resistance is associated with decreased FPGS activity, which, in turn, affects the metabolism of ZD1694 and consequently the extent and duration of in situ TS inhibition by the drug.

=> d l4 ibib abs

L4 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:588673 HCAPLUS
DOCUMENT NUMBER: 143:91000
TITLE: Reduction of toxicity of multi-targeting antifolates
INVENTOR(S): Gustavsson, Bengt; Carlsson, Goeran
PATENT ASSIGNEE(S): Biofol AB, Swed.
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005060973	A1	20050707	WO 2004-SE1955	20041222
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2550298	A1	20050707	CA 2004-2550298	20041222
EP 1699462	A1	20060913	EP 2004-809128	20041222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				
JP 2007515482	T	20070614	JP 2006-546912	20041222
US 20070249613	A1	20071025	US 2007-583508	20070515
PRIORITY APPLN. INFO.:			SE 2003-3526 A	20031222
			WO 2004-SE1955 W	20041222

AB The use of tetrahydrofolate, methylene-tetrahydrofolate and/or methyl-tetrahydrofolate, and at least one multi-targeting antifolate, for the manufacture of a pharmaceutical composition for the treatment of cancer is disclosed. By combining the multi-targeting anti-folate with tetrahydrofolate, methylene-tetrahydrofolate and/or methyl-tetrahydrofolate, it is possible to remarkably reduce toxic side-effects without diminishing the antitumor action of the drugs. A pharmaceutical composition, a kit comprising the pharmaceutical composition as well as a method for the treatment of cancer are also disclosed. An example is give of multitargeting antifolate therapy in combination the the natural isome of methylenetetrahydrofolate in experiment adenocarcinoma in rats.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 16:01:52 ON 09 JUN 2009)

FILE 'REGISTRY' ENTERED AT 16:02:08 ON 09 JUN 2009
E "PEMETREXED"/CN 25
L1 1 S E3
E "TETRAHYDROFOLATE"/CN 25

FILE 'HCAPLUS' ENTERED AT 16:03:36 ON 09 JUN 2009
L2 516 S L1
L3 8 S L2 AND (CH2FH4 OR FH4 OR TETRAHYDROFOLATE OR METHYL-TETRAHYDR
L4 1 S "MULTI-TARGETING ANTIFOLATE" OR "MULTITARGTED ANTIFOLATE"
L5 111 S "MULTI-TARGETING ANTIFOLATE" OR "MULTITARGETED ANTIFOLATE"
L6 2 S L5 AND (CH2FH4 OR FH4 OR TETRAHYDROFOLATE OR METHYL-TETRAHYDR

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	49.80	58.38
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-7.38	-7.38

STN INTERNATIONAL LOGOFF AT 16:08:07 ON 09 JUN 2009